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Noradrenaline reuptake inhibitors (NRIs) for attention deficit hyperactivity disorder (ADHD) in adults (Protocol)

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[Intervention Protocol]

Noradrenaline reuptake inhibitors (NRIs) for attention deficit hyperactivity disorder (ADHD) in adults

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of noradrenaline reuptake inhibitors (NRIs) compared with placebo or no treatment, or any active pharmacological control for treating attention deficit hyperactivity disorder (ADHD) in adults.

BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) in adults was introduced as a diagnosis in 2013 in the American *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* (DSM-5 2013), and is defined by impaired attention, hyperactivity and impulsivity that interfere with functioning or development (DSM-5 2013). The DSM-5 defines three ADHD clinical presentations based on the symptoms: predominantly inattentive (ADHD-I), predominantly hyperactive or impulsive (ADHD-H), and combined presentation (ADHD-C) (DSM-5 2013). Symptoms must occur before 12 years of age, persist for at least six months, and must lead to a significant impairment in academic, social and occupational functioning in order for a diagnosis to be made (DSM-5 2013). A similar condition, hyperkinetic disorder, is described in the *International Classification of Disease - Tenth Revision* (ICD-10 1992). A diagnosis of hyperkinetic disorder requires symptoms of inattention and hyperactivity or impulsivity, with onset before seven years of age (ICD-10 1992). Meta-analyses of epidemiological data have estimated ADHD prevalences of 3.4% in children and adolescents (Polanczyk 2015), and 2.5% in adults (Simon 2009). ADHD prevalence estimates appear not to depend on geographical location, but on the criteria used to diagnose the condition, taking into account impairment as a diagnostic criterion and

the source of information (Polanczyk 2014). However, estimates of ADHD prevalence in adults and the diagnostic validity of adult ADHD are debated (Asherson 2010; Moncrieff 2010).

Diagnostic criteria of adult ADHD require symptoms to be present from childhood, but recent population cohort studies have questioned such symptom persistence (Agnew-Blais 2016; Caye 2016; Moffitt 2015). While some follow-up studies of ADHD cohorts have reported high persistence rates into adulthood, a meta-analysis of such studies found that only 15% of children diagnosed with ADHD still fulfilled the diagnostic criteria at 25 years of age (Faraone 2006). Furthermore, a population study into the prevalence of ADHD in children and adults noted that only 5% of children with ADHD had symptoms as adults, and, conversely, that those represented only about 10% of the adult ADHD population (Moffitt 2015). In addition to these findings, longitudinal cohort studies in children who were followed up until 18 and 19 years of age have reported that only 17% of children diagnosed with ADHD in Brazil met the diagnostic criteria as adults (Caye 2016), and only 22% in the UK (Agnew-Blais 2016). These findings, however, correspond well with the high uncertainty related to making retrospective diagnoses due to a high false-positive rate (Mannuzza 2002; Suhr 2009).

To clinicians, ADHD symptoms in adults seem to be somewhat different from those in children and adolescents. Some have reported symptoms, such as reduced physical hyperactivity, restlessness or talkativeness; increasingly impaired attention, resulting in difficulties in focusing and in performing tasks; and increased impulsive behaviour, manifesting as lack of resolve, predisposition to mindless acting, and sensation seeking (Lopez 2015). To psychiatrists, persistence of individual symptoms of ADHD, particularly impaired attention and impulsivity, seem to be more common than persistence of the complete syndrome (Klein 2012).

Many psychiatric and medical comorbidities are linked to ADHD, such as substance use disorder (Kolla 2016; Pingault 2013), antisocial personality disorder (Klein 2012), and obesity (Cortese 2016). ADHD also co-occurs in about 20% of adults diagnosed with bipolar or borderline personality disorders, and often leads to sleep disturbances (Asherson 2014; Weibel 2017). The presence of ADHD symptoms among currently depressed individuals has also been described (Bron 2016), though comorbidity with mood disorders remains controversial (Klein 2012; Meinzer 2013; Torres 2015). Comorbidities such as antisocial personality, alcohol and drug abuse, as well as conduct disorder, are thought to be more common in the ADHD-H presentation, while anxiety, depression and obesity prevail in the ADHD-I presentation (Weissenberger 2017). Adults with ADHD and a comorbid medical or psychiatric disorder represent challenges for diagnosis and treatment (Katzman 2017).

The National Institute for Health and Care Excellence (NICE) guideline recommends drug treatment of adult ADHD as first-line therapy along with psychological treatment (NICE 2016). Pharmacological drugs include methylphenidate (first choice), amphetamines, and the selective noradrenaline reuptake inhibitor, atomoxetine. Other drugs are used off-label, including modafinil, guanfacine, and selective and non-selective serotonin reuptake inhibitors (Volkow 2013). Some studies have indicated promising effects of cognitive training of adults with ADHD (Stern 2016), neuro-feedback (Meyer 2015), and cognitive behavioural interventions (Jensen 2016); however, only a few studies have been conducted with these treatment modalities and more research is needed. Some people with ADHD approach non-pharmacological treatment options for various reasons, including harms or lack of benefits from medications, or a simple informed choice not to have medications (NICE 2016). Whilst dietary treatments, such as supplementary free fatty acids and the exclusion of artificial food colour, have been shown to benefit children with ADHD (Thapar 2016), there is only preliminary evidence of a beneficial effect in adults (Meyer 2015; Rucklidge 2014).

Description of the intervention

Selective noradrenaline (norepinephrine) reuptake inhibitors (NRIs) is a conditional name of psychotropic agents that inhibit the uptake of primarily norepinephrine by presynaptic nerve terminals and increase its availability in the synaptic cleft by blocking the human norepinephrine transporter (hNET) (Jamkhande 2016; Zheng 2016). Although several NRIs have been developed over the last few decades, for example, atomoxetine, reboxetine, viloxazine and maprotiline, only atomoxetine is approved by the US Food and Drug Administration (Eli Lilly 2015a), the European Medicines Agency (EMA 2017), and the Russian regulator (Roszdravnadzor 2017), in the treatment of ADHD.

Atomoxetine is the only NRI approved for the treatment of ADHD. It makes up around 9% of ADHD drug prescriptions in the UK for adults (Renoux 2016). The only meta-analysis of atomoxetine trials in adults with ADHD concluded that its harms may outweigh its benefits (Cunill 2013). A network meta-analysis compared atomoxetine to methylphenidate in adults (Bushe 2016). The analysis was sponsored by the manufacturer of atomoxetine, Eli Lilly. The analysis pooled participant- and investigator-rated symptom rating scales, although this is not recommended (Boesen 2017a), and the quality of the evidence was not assessed. Other systematic reviews have included atomoxetine and other ADHD drugs (Cunill 2013; Faraone 2010; Mészáros 2009; Peterson 2008), and have reported different effect sizes (De Crescenzo 2017). Atomoxetine is associated with a wide range of genitourinary and gastrointestinal adverse events, including erectile dysfunction, decreased libido, decreased appetite and stomach ache (Camporeale 2013; Camporeale 2015). Serious hepatic events have also been reported (Bangs 2008). It increases pulse and blood pressure in children and adults (Hennissen 2017). Atomoxetine was given a Food and Drug Administration (FDA) boxed warning in 2005 owing to an increased risk of suicidal thinking

in children and adolescents (FDA 2007), and it is associated with an increased risk of violence towards others (Moore 2010).

Reboxetine has been approved for the treatment of depression only. Two meta-analyses of its use in adults with depression reached different conclusions: one meta-analysis concluded that there were no benefits but many harms (Eyding 2010), whereas another, a technology report by the British Medicines and Healthcare products Regulatory Agency (MHRA), concluded that the benefit-to-harm ratio was positive (MHRA 2011). Reboxetine has been suggested to be useful for the treatment of ADHD but remains to be investigated (Ghanizadeh 2015).

Maprotiline is a tricyclic antidepressant that is suggested to have noradrenaline reuptake inhibitory effects and thus is included in this review. It is approved for the treatment of various mood disorders (Mylan 2014).

Viloxazine has been used previously in the treatment of depression but was withdrawn by the manufacturer for undisclosed reasons in 2002 (PubChem 2018). It is now being evaluated in clinical trials for the treatment of ADHD in children (NCT02633527).

These medicines share some similar pharmacokinetic properties that require prescribers to take special precautions to ensure their reasonably safe use in individuals, especially in combination with other drugs. Among these properties are: high protein binding (Fleishaker 2000; Sauer 2003; Scates 2000); extensive metabolism with involvement of CYP2D6 and CYP2C19 in the case of atomoxetine (Ring 2002; Sauer 2005), CYP3A4 in the case of reboxetine (Fleishaker 2000; Scates 2000), and CYP2D6 in the case of maprotiline (Firkusny 1994); and lengthy plasma half-lives. The half-life of atomoxetine depends on the individual type of metabolism and ranges from 5.2 hours in extensive metabolisers to over 21 hours in poor metabolisers (Eli Lilly 2015b). The elimination half-life of reboxetine is about 12 to 13 hours following the administration of single and multiple doses (Edwards 1995; Pellizzoni 1996). The average half-life of maprotiline is 43 hours after single or repeated doses (Wells 1981).

These medicines also share adverse events, including suicidality and withdrawal problems. Although Bangs 2014 did not find a greater risk of suicidality, suicidal ideation has been highlighted in the product information for reboxetine and atomoxetine (Edronax 2017; Eli Lilly 2015b). Rapid cessation of atomoxetine (and other NRIs) can lead to problems with withdrawal symptoms (Mental Health Daily 2017; Strattera 2017; Wernicke 2004). This is in line with atomoxetine's classification position in the WHO ATC/DDD Classification system, in which atomoxetine along with amphetamine, methylphenidate, modafinil and their derivatives are classified as 'centrally acting sympathomimetics', reboxetine and viloxazine as 'other antidepressants', and maprotiline as a 'non-selective monoamine reuptake inhibitor' (WHO ATC/DDD Classification system).

How the intervention might work

It has been suggested that the noradrenergic system is involved in the regulation of higher cortical functions, such as attention, alertness and vigilance (Arnsten 2005; Biederman 1999; Chamberlain 2013; Levy 2009). This allows for the hypothesis of potential beneficial effects of drugs blocking the human norepinephrine transporter for the treatment of ADHD, thought to be caused by dysfunction of the noradrenergic network (Biederman 1999; Heal 2009). Noradrenaline (norepinephrine) has pronounced effects on the prefrontal cortex, which is important in the regulation of behaviour and thinking (Arnsten 2012). Deficits in the inhibitory frontostriatal noradrenergic connections of the dopaminergic striatal structures may lead to the dysregulation of attention and action (Zametkin 1987), and the insufficiency of prefrontal cortex circuits in people with ADHD has been corroborated by neuropsychological, structural and functional studies (Arnsten 2005; Arnsten 2012; Faraone 2015). Nevertheless, whether norepinephrine would improve or impair the prefrontal cortex function depends on the amount of norepinephrine that is available; moderate levels of norepinephrine have been found to improve prefrontal cortex function through α2A-adrenoreceptors, whereas high levels of norepinephrine, associated with stress, hamper prefrontal cortex function through α1-adrenoreceptors (Arnsten 2005). Noradrenaline reuptake inhibitors specifically inhibit the presynaptic uptake of norepinephrine by the human norepinephrine transporter, thereby increasing the amount of norepinephrine available in the synaptic cleft. The effects of NRIs in the treatment of ADHD is therefore suggested to be mediated by the noradrenergic transmission and improving the functions of the prefrontal cortex (Arnsten 2005; Bymaster 2002; Swanson 2006).

The benefits of long-term ADHD treatment (primarily stimulants) are uncertain. Follow-up from the Multimodal Treatment of ADHD (MTA) study in children has not indicated evidence of benefits from long-term pharmacological treatment on ADHD symptom severity (Swanson 2017), or on functional outcomes, such as school grades, indictable offences or psychiatric hospitalisations (Jensen 2007; Molina 2009). However, increased rates of delinquency (Molina 2007), and impaired growth (Swanson 2017), have been observed in the treatment group. Two European cohort studies with six-year follow-up in adolescents (Lieshout 2017), and adults (Edvinsson 2018), made similar conclusions about the lack of long-term medication effects on ADHD symptom severity.

Why it is important to do this review

ADHD is a condition leading to significant expenses. In the Netherlands, the ADHD annual related cost estimates ranged from EUR 1 billion to EUR 1.5 billion, and included additional healthcare expenses, educational and social services, and productivity loss by family members (Le 2014). In Italy, pharmacological therapy was found to be less expensive than psychological interventions; the annual median drug cost per person amounted to EUR 98,

while the median psychological therapy costs amounted to EUR 590 (Casadei 2017).

ADHD has been recognised as a controversial issue for more than 20 years, as reported in the National Institutes of Health's (NIH) consensus statement (NIH 1998). The ongoing debate on the diagnosis, etiology and pharmacological treatment of ADHD has continued for a long time; some argue that ADHD is a biological disorder that responds well to central stimulants (Barkley 2002), while others argue that there is little evidence to support these assumptions (Timimi 2004). The use of ADHD medicines in children and adults is rising steadily (Renoux 2016), which has led to concerns of ADHD over-diagnosis and over-treatment (Paris 2015). The International Narcotics Control Board has been concerned about the growing global consumption of methylphenidate for over 20 years now (INCB 1996; INCB 2015), and there are increasing concerns about overuse of methylphenidate in children (FDA 2011).

Three Cochrane Reviews raised concerns about the use of methylphenidate - currently the drug of choice for ADHD - and amphetamines.

1. Storebø 2015 concluded that, for children and adolescents with ADHD, there was only very low-quality evidence that it might improve symptoms compared to placebo or no treatment, and that there was evidence of a range of adverse events.
2. Castells 2011 compared amphetamines to placebo in the treatment of ADHD amongst adults. They found that, whilst amphetamines appeared to improve ADHD symptoms in the short term, the drug did not have higher retention in treatment compared to placebo. Amphetamines were also associated with a higher risk of withdrawal from studies due to adverse events, and the authors suggested that there could be a blinding failure in the included trials, leading to an overestimation of amphetamine's benefits.
3. Punja 2016 examined the effectiveness of amphetamines for children and adolescents with ADHD and found similar shortcomings of the included trials, rating the quality of the evidence as "very low" for most of the outcomes examined.

Considering the concerns raised and the limitations of ADHD trials in children and adults, a thorough assessment of the benefits and harms of NRIs and their potential role in the treatment of adult ADHD is warranted. This will be the first published review of NRIs for adult ADHD and is one of a series of Cochrane Reviews assessing pharmacological agents in people diagnosed with ADHD.

OBJECTIVES

To assess the benefits and harms of noradrenaline reuptake inhibitors (NRIs) compared with placebo or no treatment, or any active pharmacological control for treating attention deficit hyperactivity disorder (ADHD) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults aged 18 years and older, diagnosed with attention deficit hyperactivity disorder (ADHD) before or after 18 years of age according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) - *Third Edition (Revised)* (DSM-III-R 1987); *Fourth Edition (Text Revision)* (DSM-IV-TR 2000); *Fifth Edition* (DSM-5 2013); or the *International Classification of Diseases - Tenth Revision* (ICD-10 1992). We will include studies with participants both under and over 18 years of age provided we can obtain the data pertaining to those $\geq$ 18 years.

We will exclude studies using the Ninth Edition of the ICD (ICD-9 1978), since the ICD-9 is not based on operationalised criteria; it contains no diagnostic criteria, only disease names. We will not consider psychiatric comorbidity as exclusion criteria.

Types of interventions

Noradrenaline (norepinephrine) reuptake inhibitors (NRIs), such as atomoxetine, maprotiline, reboxetine, and viloxazine, in any formulation and at any dose, compared with placebo or no treatment, or any active pharmacological control. We will allow cointerventions (for example, cognitive behavioural therapy) provided they are given to both groups, to enable pair-wise comparisons.

Types of outcome measures

We will include studies that meet our inclusion criteria regardless of whether or not they report on the outcomes listed below.

Primary outcomes

1. Functional outcomes: academic adherence and job adherence, assessed by numbers of days lost from work or studies (Philipsen 2015), marital status, delinquency, traffic accidents, and other emergencies as characteristics of daily functioning.
2. Serious adverse events, defined according to the International Council for Harmonisation (ICH) guideline, as any event that is fatal or life-threatening, requires hospitalisation or prolongation of existing hospitalisation or a change of treatment regimen, results in persistent or significant disability/incapacity, or presents as a congenital anomaly or birth defect

(ICH 2003). We will consider all other adverse events to be non-serious.

3. Withdrawal from treatment for any reason.

Secondary outcomes

1. Self-rated ADHD symptoms, measured using a validated rating scale; for example, the Connors' Adult ADHD Rating Scale (CAARS; Conners 1999).
2. Investigator-rated ADHD symptoms, measured using a validated rating scale; for example, the CAARS (Conners 1999).
3. Observer-rated ADHD symptoms, measured using a validated rating scale; for example, the CAARS (Conners 1999).
4. Any non-serious adverse events. We will provide descriptive information from the trials on adverse events, including the total number of people experiencing the event. We will provide a detailed description of potential limitations of reporting adverse events, such as not presenting any adverse event data if the rate happens to be below some predefined threshold.
5. Quality of life, measured by validated psychometric scales such as the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Mick 2008).

We will use data with the longest possible follow-up. We expect to be able to use data from three timeframes: short-term (up to 6 months), medium-term (6 months to 12 months), and long-term (more than 12 months). See also Unit of analysis issues.

Search methods for identification of studies

Electronic searches

We will search the electronic databases and trials registers listed below.

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library, and which includes the Cochrane Developmental, Psychosocial and Learning Problems Group Specialized Register.
2. MEDLINE Ovid (1946 onwards).
3. MEDLINE Ovid In-Process & Other Non-Indexed Citations (current issue).
4. MEDLINE Ovid E-Pub Ahead of Print (current issue).
5. Embase Ovid (1974 onwards).
6. *Cochrane Database of Systematic Reviews* (CDSR; current issue), part of the Cochrane Library.
7. Database of Abstracts of Reviews of Effects (DARE; current issue), part of the Cochrane Library.
8. PsycINFO Ovid (1806 onwards).
9. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 onwards).
10. Science Citation Index - Expanded Web of Science (1970 onwards).
11. Conference Proceedings Citation Index - Science Web of Science (1990 onwards).
12. e-library Russia (elibrary.ru; 1998 onwards).
13. EastView Russia (online.ebiblioteka.ru/index.jsp; 2006 onwards).
14. LILACS Bireme Virtual Health Library (Latin American and Caribbean Health Sciences Literature; lilacs.bvsalud.org/en).
15. Networked Digital Library of Theses and Dissertations (NDLTD; search.ndltd.org).
16. ClinicalTrials.gov (clinicaltrials.gov).
17. EU Clinical Trials Register (www.clinicaltrialsregister.eu).
18. ISRCTN Registry (www.isrctn.com).
19. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en).

We will not limit the searches by publication date, publication status, or language.

We will search MEDLINE using the strategy in Appendix 1, which includes the Cochrane highly sensitive search strategy for identifying randomised trials (Lefebvre 2011). We will modify this strategy for use with the other databases.

Searching other resources

We will search the reference lists of included studies and relevant reviews to find additional studies not identified by the electronic searches (Electronic searches). We will contact the authors of the included trials, the main medicine agencies (European Medicines Agency (EMA) and the US Food and Drug Administration (FDA)), and pharmaceutical companies that manufacture NRIs, to request any additional or unpublished data. We will also search relevant conference proceedings, the Yale University Open Data Access (YODA) project (yoda.yale.edu), and national clinical guidelines such as the National Institute for Health and Care Excellence (NICE) guidelines (nice.org.uk), Danish National Clinical Guidelines (sundhedsstyrelsen.dk), and the Russian National Standards of Care (rosminzdrav.ru).

Data collection and analysis

Selection of studies

Using Covidence 2017, at least two review authors (FDC, LEZ, EVY, YCK, MC) will independently screen the titles and abstracts of all records yielded by the searches, discarding those that are clearly irrelevant. Next, we will obtain the full texts of all potentially eligible papers, including those for which further information is needed to determine relevance. Working in pairs, two review authors (FDC, LEZ, EVY, YCK, MC) will independently assess these reports against the inclusion criteria described above (Criteria for considering studies for this review), again using Covidence 2017. At both stages, review authors will compare their resulting

independent assessments, resolving any disagreements by discussion, and seeking arbitration with the rest of the review team if necessary. We will provide reasons for excluding relevant studies in the 'Characteristics of excluded studies' tables. We will record our decisions in a study flow diagram (Moher 2009).

Data extraction and management

At least two review authors (FDC, LEZ, EVY, YCK, MC) will independently extract data using Covidence 2017. We will extract data on the methods, participants, interventions, and outcomes. We will compare the data extracted, resolving any differences by referring to the original articles and through discussion. If the data are only available as graphs, we will extrapolate the data with Plot Digitizer software (Rohatgi 2018) and contact the study authors for clarification.

We will extract data to allow analyses based on the intention-to-treat (ITT) approach (including all participants in the groups to which they were originally randomly allocated), and will present the data in the 'Characteristics of included studies' tables. We will calculate the percentage loss to follow-up and present it in the 'Risk of bias' table.

For binary outcomes, we will extract the number of participants with the event in each group. For continuous outcomes, we will use means and standard deviations (SDs) for each group and convert reported data, when necessary, using statistical conversions (Higgins 2011a). If studies report medians and interquartile ranges, and if the data are skewed rather than normally distributed, we will attempt to collect appropriate data summaries from the trialists, or acquire individual participant data (IPD). We will decide on appropriate data summaries and analysis strategies for the IPD according to the situation and based on consultation with a statistician from the Cochrane Developmental, Psychosocial and Learning Problems editorial board (Higgins 2011a).

One review author will enter the data into Review Manager 5 (RevMan 5) (Review Manager 2014), and another review author will proofread the entered data for accuracy.

Assessment of risk of bias in included studies

At least two review authors (FDC, LEZ, EVY, YCK, MC) will independently assess each included trial for risk of bias using Cochrane's 'Risk of bias' tool (Higgins 2017). The 'Risk of bias' tool consists of seven domains, which we present below in a form of questions to be answered for each included study by the review authors.

1. Random sequence generation (selection bias): was the sequence generated adequately (e.g. computer-generated) or inadequately (e.g. using the day of study enrolment to allocate participants)?
2. Allocation sequence concealment (selection bias): was the implementation of the randomisation sequence adequate (e.g. central allocation by a third party) or inadequate (e.g. open allocation or using non-opaque envelopes)?
3. Blinding of participants and personnel (performance bias): were the methods used to maintain the blinding of participants and personnel, other than those measuring outcomes during the study, adequate or inadequate (i.e. due to the drug effects)?
4. Blinding of outcome assessment (detection bias): were the methods used to maintain the blinding of those measuring outcomes during the study adequate or inadequate (i.e. due to the drug effects)?
5. Incomplete outcome data (attrition bias): were missing data adequately addressed, and were dropout rates balanced?
6. Selective outcome reporting (reporting bias): were the primary and secondary outcomes fully reported or not?
7. Other potential sources of bias: was the study free of other potential sources of bias, such as baseline differences?

For each domain, review authors will assign ratings of low, high or unclear risk of bias (Higgins 2017), resolving any disagreements through discussion and, where necessary, with input and advice from the remaining review authors and the review group (Cochrane Developmental, Psychosocial and Learning Problems). We will consider studies that receive a judgement of high risk of bias in one or more domain(s) to be at high risk of bias overall; those that receive a judgement of low risk of bias in all domains to be at low risk of bias overall; and those that receive a judgement of unclear risk of bias in one or more domains to be at unclear risk of bias overall. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will use Covidence 2017 to conduct the 'Risk of bias' assessment and to facilitate consensus in the case of disagreements.

Additional domains for 'Risk of bias' assessment in ADHD trials

We will use three, additional domains for ADHD drug trials that have been developed by the Cochrane Nordic author team (with their permission), to assess three specific study features that affect trials' external validity (Boesen 2017b). These three domains are covered by the 'indirectness' domain in the GRADE tool (Schünemann 2017), and it is important to highlight these study features separately and assess their impact on the potential for generalisation of the trial results. As these additional domains describe features concerning external validity, they should not be confused with the 'Risk of bias' tool's regular domains that evaluate a trial's internal validity.

1. Psychiatric comorbidity

Adults with a diagnosis of ADHD often have psychiatric comorbidity (Sobanski 2006). Excluding participants with psychiatric comorbidity before randomisation will reduce the external valid-

ity of an ADHD trial (Surman 2010), and may cause an overestimation of the potential treatment effects of a study drug (Pliszka 1989; Sobanski 2007).

1. Low risk: participants with psychiatric comorbidity were included unless NRI treatment was contraindicated (e.g. suicidal or psychotic)
2. Unclear risk: there was no, or an unclear, description of whether or not participants with psychiatric comorbidity were included
3. High risk: participants with psychiatric comorbidities were excluded before, or after, randomisation

2. Responder selection

Some people do not benefit from NRIs or may even get worse and experience adverse events. These are known as "non-responders" (Chiarenza 2016). From an ethical standpoint, it may not be acceptable to enrol participants who are known not to benefit or who experience harms from drug treatment. However, excluding these people from randomisation will lead to an overestimation of benefits and an underestimation of harms, compared to a treatment-naive population. This will most likely also occur if previously medicated participants who are known to benefit from the treatment are enrolled. This study design is misleadingly called an "enriched design" (FDA 2012).

1. Low risk: participants were treatment-naive
2. Unclear risk: there was no, or an unclear description, of the exclusion criteria or of previous NRI or other typical stimulant ADHD drug use
3. High risk: non-responders (or similar) were excluded before randomisation (we will also rate trials that allowed previously-treated participants at high risk of responder selection)

3. Pre-randomisation ADHD drug treatment

Discontinuing atomoxetine or another NRI treatment can lead to withdrawal symptoms (Mental Health Daily 2017; Strattera 2017; Wernicke 2004), similar to those associated with typical stimulant drugs (Cox 2008). If participants are washed out of their ADHD treatment (NRI or typical stimulant drugs), and more so if they are not washed out prior to randomisation, such withdrawal or abstinence symptoms may develop in those randomised to placebo and this could be interpreted as a worsening of their ADHD symptoms.

1. Low risk: participants were treatment-naive (no previous ADHD drug treatment)
2. Unclear risk: there was no, or an unclear, description of whether randomised participants were treatment-naive
3. High risk: ADHD drugs were stopped just before randomisation, with or without a washout

Measures of treatment effect

Dichotomous data

For dichotomous data, we will compute a risk ratio (RR) and present this with 95% confidence intervals (CIs). We will not extract composite outcomes such as dichotomous responder rates that consist of several outcomes combined.

Continuous data

For continuous data measured on the same scale, we will extract mean change or endpoint data in order to calculate a mean difference (MD), and present this with 95% CIs. For continuous outcomes measured on different scales, we will extract mean change from baseline or endpoint data and the corresponding SDs or standard errors (SEs) to calculate a standardised mean difference (SMD), and present this with 95% CIs.

Unit of analysis issues

Cluster-randomised trials

We anticipate that authors of cluster-randomised trials, which randomise groups as opposed to individuals, will have controlled for the clustering effect in their results. If we are unclear from the trial report on application of appropriate controls for clustering, we will contact the trial authors for further details. If the trial authors report data from cluster-randomised trials as if they randomised individuals and not clusters, we will request IPD and calculate an estimate of the intracluster correlation coefficient (ICC). If we are unable to get access to IPD, we will use external ICC estimates based on studies in similar populations.

We plan to use the ICC to obtain approximate correct analyses, as described in Section 16.3.4 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will combine the effect estimates from non-clustered and clustered trials to obtain an overall estimate of effect, using the generic inverse variance method in RevMan 5 (Higgins 2011b; Review Manager 2014). If we do not get enough data to control for clustering as described, we will enter the data into RevMan 5 using individuals as the unit of analysis and then conduct a sensitivity analysis to assess the effect of the inadequately controlled cluster-randomised trials on the effect estimate (see Sensitivity analysis).

Cross-over trials

We will only use first-period data from any cross-over trial that meets our inclusion criteria, to avoid the risk of carry-over effect, treating them as parallel group trials.

Trials with multiple arms

If we identify trials with multiple arms in the primary analysis, we will combine results across all eligible experimental groups (e.g. all NRIs) and compare them to the combined results of all eligible control groups, thereby making single, pair-wise comparisons. If this strategy results in a loss of important information or prevents investigation of significant sources of heterogeneity, we will analyse each arm separately (against a common control group) but divide the sample size for common comparator groups accordingly, in proportion to each comparison (Higgins 2011b, section 16.5.4), thereby avoiding any double-counting of participants.

Studies with multiple time points

We will categorise various time points used in the trials into three groups: short-term (up to six months), medium-term (six to 12 months) and long-term (more than 12 months). This will allow us to identify any decrease in effects of drugs over time and will help to avoid multiple analyses. If a study report presents multiple sets of data within the same predefined outcome period, we will extract data with the longest follow-up time.

Dealing with missing data

A drug-class review found that the reporting of ADHD drug trials is often characterised by missing data (McDonagh 2011).

We will contact the study authors and request that they provide any missing data, including group means and SDs, details of dropouts, and details of interventions (e.g. dose and frequency). We will also contact the study authors for additional information in cases where a study only reports the outcome for those participants who completed the trial or who adhered to the protocol. If we are unable to obtain the missing data from the study authors, we will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

We intend to apply an ITT analysis for all missing data, imputing missing data wherever possible. For dichotomous data considered not missing at random, we will assume participants in the experimental group experienced a favourable outcome, as in the best-case scenario (for example, there are less participants in the experimental group with poor functional outcomes, or with serious adverse events, or withdrawn from treatment for any reason), and all participants in the control group experienced a less favourable outcome (there are more participants in the control group with the above described outcomes, accordingly) - or vice versa as in the worst-case scenario. We will impute missing continuous data assuming a fixed mean difference between the actual mean for the missing data and the assumed mean by the analysis (e.g. if the missing data in the NRI arm had averaged two units greater than the observed data in the NRI arm, and the missing data in the control arm (placebo or no treatment; or active control as a separate comparison) had averaged two units *less* than the observed data in the control arm), as recommended by Higgins 2011b. We will examine the robustness of these decisions by conducting sensitivity analyses (see Sensitivity analysis).

We will carefully describe all missing data and rates of attrition for each included study (in the 'Risk of bias' tables), and, in each case, will consider the extent to which data could be considered 'missing at random' and could alter the results and conclusions of the review.

We will specify the methods used to impute missing data in the 'Characteristics of included studies' tables. If imputation is not possible, we will analyse the available data only and describe the reasons for this in the text. We will address the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining differences in participants of individual trials, interventions, outcomes and settings; and whether these differences are related to differences in results of the individual trials. We will pay special attention to three specific trial features: exclusion of people with psychiatric comorbidity; exclusion of people who did not tolerate or respond well to previous ADHD medication (so-called non-responders); and the timing at which pre-randomisation ADHD drug exposure was stopped.

We will assess methodological heterogeneity by conducting 'Risk of bias' assessments using the Cochrane 'Risk of bias' tool (Higgins 2017).

We will test for statistical homogeneity or heterogeneity of effect sizes between studies by inspecting the forest plots and using the Chi^2 test ($P < 0.10$). We will also use the I^2 statistic (Higgins 2003), and will consider values between 30% and 60% to denote moderate levels of heterogeneity (Deeks 2017).

We will explore reasons for heterogeneity by conducting subgroup (see Subgroup analysis and investigation of heterogeneity), and sensitivity analyses (see Sensitivity analysis).

We will also report tau^2 as an estimate of between-study variation when using the random-effects model.

Assessment of reporting biases

We will use funnel plots, which plot effect sizes against their SEs (Egger 1997), to examine asymmetry that may have been caused by publication bias and other small study effects, providing 10 or more trials report data on a given outcome (Sterne 2017).

We will test for outcome switching by comparing predefined primary and secondary outcomes in protocols and trial registries with published outcomes (Compare 2016). If a protocol has not been published, we will request it from trial authors to enable such comparison. If we are unable to obtain the protocol, we will add this fact as an argument for assessing reporting bias at a higher risk of bias. We will examine reporting biases by assessing the potential

risks of bias in each study (e.g. sponsors of research, research teams involved). See Assessment of risk of bias in included studies.
We will assess selective outcome reporting using the Outcome Reporting Bias in Randomised Controlled Trials (ORBIT) tool (Kirkham 2010). We will look for arbitrary thresholds for adverse event reporting (i.e. a threshold representing a certain percentage of participants with adverse events, which is to be reached for adverse events to be reported), and will consider the use of such thresholds as selective outcome reporting.

Data synthesis

As we anticipate clinical, methodological and statistical heterogeneity (McDonagh 2011), we will use the random-effects (DerSimonian and Laird) model for meta-analysis (DerSimonian 1986), with inverse variance weighting. We will undertake analyses according to the ITT approach. We will analyse the data using RevMan 5 (Review Manager 2014). However, when no significant clinical, methodological or statistical heterogeneity is present, we will synthesise data using a fixed-effect model (the Mantel-Haenszel method; Mantel 1959), as set by default in Review Manager 2014, and compare results obtained with the random-effects and fixed-effect models in a Sensitivity analysis. This will also allow us to avoid the influence of small study effects. We will combine the experimental groups in studies with multiple arms using different NRIs and differing dosages of the study drugs, as already described (see Measures of treatment effect).

Summarising and interpreting findings

We will create 'Summary of findings' tables using our Primary outcomes and Secondary outcomes for the comparisons: NRIs versus placebo or no treatment; and NRIs versus active pharmacological control (other pharmacological agents). We will include data at the following time points, where available: short-term (up to 6 months), medium-term (6 months to 12 months), and long-term (more than 12 months). We will construct the table using GRADE Profiler software (GRADEpro 2015), importing data from RevMan 5 (Review Manager 2014). Using the GRADE approach (Schünemann 2017), at least three independent review authors (from FDC, LEZ, EVY, YCK, MC) will evaluate the quality of evidence for each outcome as high, moderate, low or very low, according to the presence of the following five criteria: risk of bias, publication bias, imprecision, inconsistency and indirectness (GRADE Handbook 2013). We will use these ratings to guide our conclusions.

Subgroup analysis and investigation of heterogeneity

We plan to conduct the following subgroup analyses to investigate potential sources of heterogeneity.

1. Psychiatric comorbidity (trials that excluded participants with psychiatric comorbidity versus trials that did not).
2. Treatment status (studies with treatment-naive participants versus studies with previously treated participants).
3. Unpublished studies (unpublished studies versus published studies).
4. Vested interests (industry sponsored trials versus non-industry sponsored trials).
5. Comparator (trials testing NRI versus placebo/no treatment; and trials testing NRI versus active pharmacological control; we will also test the differences between the subgroups).

Sensitivity analysis

We will perform sensitivity analyses to test the robustness of the results. To this end, we will:

1. exclude studies at high risk of selection, performance, detection or reporting bias; or restrict the analysis to studies with an overall low risk of bias;
2. assess the effect of the inadequately controlled cluster-randomised trials on the effect estimate;
3. exclude studies with a cross-over design, to assess the effect of trial design;
4. impute missing dichotomous data according to a worst-case (all participants with missing outcomes in the intervention group have poor outcomes, and in the control group have good outcomes) scenario;
5. impute missing dichotomous data according to a best-case (all participants with missing outcomes in the intervention group have good outcomes, and in the control group have poor outcome) scenario;
6. impute missing continuous data; and
7. use the fixed-effect model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 "attention deficit and disruptive behavior disorders"/
2 attention deficit disorder with hyperactivity/
3 conduct disorder/
4 ADHD.tw,kf.
5 ADDH.tw,kf.
6 ADHS.tw,kf.
7 ("AD/HD" or HKD).tw,kf.
8 TDAH.tw,kf.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kf.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kf.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kf.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$).tw,kf.
14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kf.
15 (hyperactiv$ or hyper-activ$).tw,kf.
16 or/1-15
17 Adrenergic Uptake Inhibitors/
18 Antidepressive Agents, Second-Generation/
19 selective noradrenaline re-uptake inhibitor$.mp.
20 SNR$1.mp.
21 Atomoxetine Hydrochloride/
22 Atomoxetin$.mp.
23 Strattera.mp.
24 Morpholines/
25 Reboxetine.mp.
26 Edronax.mp.
27 Vestra.mp.
28 Maprotiline/
29 Maprotiline.mp.
30 Ludiomil.mp.
31 noradrenaline re-uptake inhibitor$.mp.

32 noradrenaline reuptake inhibitor$.mp.
33 norepinephrine re-uptake inhibitor$.mp.
34 norepinephrine reuptake inhibitor$.mp.
35 NARI$1.tw,kf.
36 NRI$1.tw,kf.
37 Viloxazine/
38 Viloxazine.mp.
39 Vivalan.mp.
40 or/17-39
41 randomized controlled trial.pt.
42 controlled clinical trial.pt.
43 randomi#ed.ab.
44 placebo$.ab.
45 drug therapy.fs.
46 randomly.ab.
47 trial.ab.
48 groups.ab.
49 or/41-48
50 exp animals/ not humans.sh.
51 49 not 50
52 16 and 40 and 51

CONTRIBUTIONS OF AUTHORS

Franco De Crescenzo and Liliya Eugenevna Ziganshina drafted the protocol and have overall responsibility for the review. All authors contributed to writing the protocol.

DECLARATIONS OF INTEREST

Franco De Crescenzo: none known.

Liliya Eugenevna Ziganshina is the Director of Cochrane Russia. It should be noted that no funding was administered for this review.

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